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Review

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New Horizons for Old Drugs and Drug Leads

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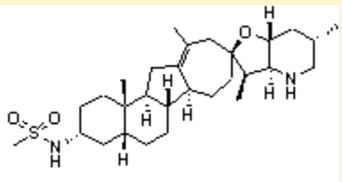
34 Cyclopamine



35 IPI-926

ABSTRACT: There is mounting urgency to find new drugs for the treatment of serious infectious diseases and cancer that are rapidly developing resistance to previously effective drugs. One approach to addressing this need is through drug repurposing, which refers to the discovery of new useful activities for "old" clinically used drugs through screening them against relevant disease targets. A large number of potential drug that, for various reasons, have failed to advance to clinical and commercial use can be added to the candidates available for such purposes. The application of new techniques and methodology developed through the impressive progress made in multidisciplinary, natural product-related research in recent years should aid substantially in expediting the discovery and development process. This review briefly outlines some of these developments as applied to a number of selected natural product examples, which may also include advances in chemical synthesis of derivatives with extended biological activities.

INTRODUCTION

Throughout most of history, Nature, especially plants, has provided a source of medicines for the treatment of a wide spectrum of diseases. Starting in the early 1800s, advances in scientific knowledge led to the discovery of pure bioactive compounds, commonly referred to as natural products (NPs). Among the first reported examples were strychnine, morphine, atropine, quinine, and colchicine in the early 1800s. These isolations were followed by what can be regarded as the development of the first commercial, pure natural product, morphine, by E. Merck in 1826, and the first semisynthetic, pure drug based on a natural product, aspirin, by Bayer in 1899. This was the start of a new era in medicine, where drugs could be purified from plants and administered in precise dosages, independent of the source or age of the plant material.[1,2]

The next milestone was the report by Fleming in 1929 of the serendipitous discovery of penicillin from the filamentous fungus *Penicillium notatum*, which ushered in the "Golden Age of Antibiotics", as the time period from the 1940s to the 1970s was christened. This heralded an extensive investigation of microbes, mainly by pharmaceutical companies, as sources of novel antibiotics and led to the discovery not only of the penicillins but a host of other antibacterial antibiotics, including the cephalosporins, tetracyclines (e.g., doxycycline), aminoglycosides (e.g., streptomycin), glycopeptides (e.g., vancomycin), lipopeptides (e.g., daptomycin), and macrocyclic compounds such as erythromycin.[1,3] In keeping with the theme of this review, it is estimated that well over 20 000 penicillin- and cephalosporin-based molecules have been produced by semisynthesis and total synthesis, starting with modification of the fermentation product 6-aminopenicillanic acid or the corresponding cephalosporin, 7-amino-cephalosporanic acid, both of which can be produced by simple chemical or biochemical deacylation from penicillin or cephalosporin C.[1,3,4] Details of some of the new and more effective drugs to emerge from these studies, and studies on the other antibacterial antibiotic classes mentioned above, are given in refs 3 and 4. Microbes have also been the source of other anti-infective drugs in the form of antibiotics having antifungal (e.g., amphotericin, nystatin) and antiparasitic (e.g., ivermectin, fumagillin) activities.[1,3]

Microbes have provided further indispensable models for the development of the anticholesterolemic class of drugs, widely known as statins, and a broad range of so-called antitumor antibiotics, which are among the most important of the cancer chemotherapeutic agents. The discovery of the fungal metabolites mevastatin (compactin) and lovastatin as inhibitors of HMG-CoA reductase led to the development of synthetic statin analogues, such as atorvastin (Lipitor) and simvastatin (Mevacor), all containing the essential natural product "warhead" resembling mevalonic acid. These agents have ranked as some of the best-selling drugs of all time.[3,4] The antitumor antibiotics include the ansamycins (e.g., geldanamycin), the anthracyclines (e.g., doxorubicin), the glycopeptidic bleomycins A2 and B2 (blenoxane), the peptolides (e.g., dactinomycin), the enediynes (e.g., calicheamicin), the epothilones (e.g., ixabepilone), the mitosanes (e.g., mitomycin

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C), the rapamycins (e.g., everolimus), and the staurosporines (e.g., rebeccamycin). The discovery and development of these drugs and their analogues are discussed in refs 3, 5, and 6. Rapamycins are also important immunosuppressive drugs,[4,7] complementing the role of another microbial metabolite, cyclosporine, of import in this area.[2]

During the era of intensive research into the discovery of novel antibiotics from microbial sources outlined above, starting in 1940s, plants continued to be investigated as a source of novel medicinal agents, with the focus being mainly on the discovery of novel anticancer drugs.[8,9] Thus, the vinca alkaloids, epipodophyllotoxins, taxanes, and camptothecins were discovered and developed into highly effective cancer chemotherapeutic agents, and many bioactive plant-derived metabolites were isolated as promising leads for anticancer drug development.[5,6,8,9]

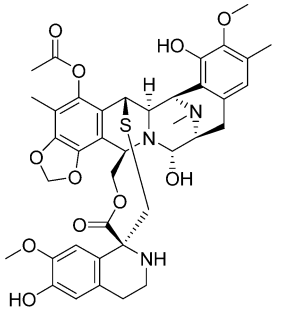
Unlike terrestrial plants, marine organisms do not have a significant history of use in traditional medicine, and thus, until relatively recently, they had not received the same attention as possible sources of bioactive metabolites. Nevertheless, considering that the world's oceans cover more than 70% of the earth's surface, and 32 of the 33 animal phyla are represented in aquatic environments, oceans represent an enormous resource for the discovery of potential chemotherapeutic agents.[10,11] Probably the first significant discoveries from a marine source were the bioactive nucleosides spongouridine and spongothymidine, isolated from a Caribbean sponge in the early to mid-1950s. The presence of arabinose as the sugar moiety in these compounds changed the then current dogma that only nucleosides with ribose or deoxyribose moieties were bioactive. Thus, they can be considered as the prototypes of the multiple modified nucleoside analogues containing a variety of acyclic and cyclic sugar entities, synthesized in the quest for more effective antiviral and antitumor agents.[1,4,10]

Another important class of marine-derived bioactive agents is the conotoxins, isolated from venomous cone snails (genus *Conus*).[2,11] The venom contains multiple toxic polypeptides generally delivered via a harpoon-like hollow tooth, thereby paralyzing prey by targeting the neuromuscular system. Following several decades of research and development starting in the 1970s, ziconotide, a synthetic form of ω-conotoxin MVIIA isolated from *Conus magus*, became the first marine-derived drug to be approved by the U.S. Food and Drug Administration (FDA), with approval being granted in 2005 for the treatment of chronic pain under the trade name Prialt.[11]

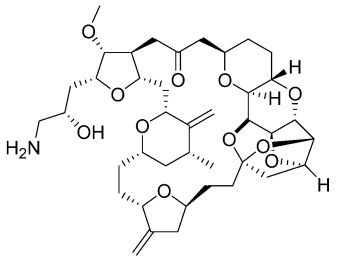
The marine environment has been a productive source of potential anticancer agents. Ecteinascidin-743 (ET-743/trabectedin/Yondelis, **1**) was the first marine-derived anticancer drug to be approved for commercial use in 2007, followed by eribulin mesylate (E7389/Halaven, **2**), a synthetic analogue of halichondrin B, in 2010, and SGN-30 (brentuximab vedotin/Adcetris), an antibody drug conjugate incorporating monomethyl auristatin E (**3**), a synthetic analogue of dolastatin 10, conjugated to the humanized anti-CD30 monoclonal antibody, which received accelerated approval from the FDA in August 2011 for the treatment of Hodgkin's lymphoma. Agents currently in clinical trials against cancer include aplidine (**4**, plitidepsin/dehydrodidemnin B), kahalalide F (**5**), PM10450 (**6**, zalypsis) and PM1183 (**7**, lurbinectedin), both chemically related to ET-743, and PM060184 (B), a newly isolated antimitotic agent from the sponge *Lithoplocamia lithistoides* and synthesized by PharmaMar scientists.[12] Eisai had a hemiasterlin derivative, E-7974 (**9**), in phase I clinical trials, but this now appears to have been removed from trials as of early September 2013.

Salinosporamide A (**10**), which was the first compound isolated from a marine microbe and was listed as being in phase I heading for phase II trials, may not be a clinical candidate at the time of writing due to the demise of Nereus Pharmaceuticals in the late summer of 2013. Clinical trials have been terminated for several agents, including KRN-7000, TZT-1027 (auristatin PE/soblidotin) and ILX651 (synthadotin), didemnin B, discodermolide, HT-286, a synthetic hemiasterlin analogue, and cryptophycin 52, a synthetic analogue of the cyanobacterial metabolite cryptophycin 1. Cematodin (LU-103793), which was in phase II clinical trials, may well be being considered as a warhead, but no details other than a paper in 2012 have been published.[13] Details of the discovery and development of these agents, together with several others in preclinical development, are given in refs 5, 6, 10, 11, 14, and 15. Thus, natural products have been, and continue to be, an invaluable source of novel drugs[16−19] and drug leads[20] for the treatment of many diseases.

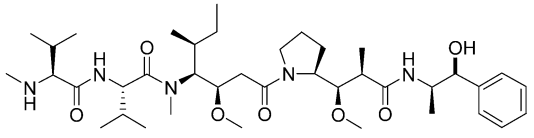
Chart 1



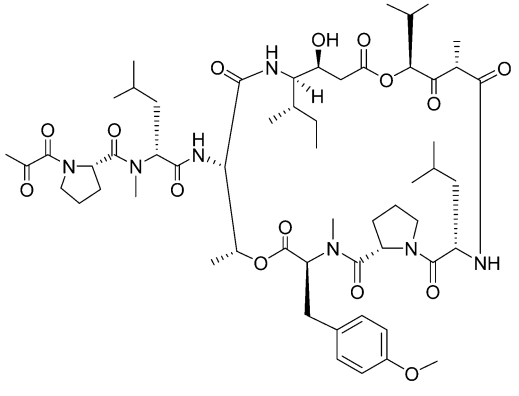
1 Ecteinascidin 743



2 E7389 (Eribulin)



3 Vedotin; monomethylauristatin E



4 Aplidine

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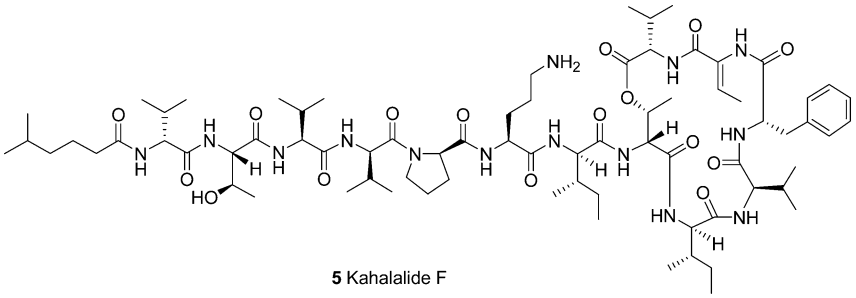
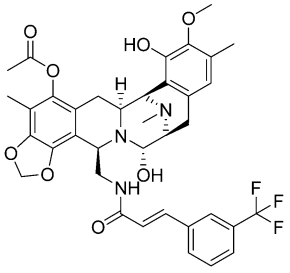
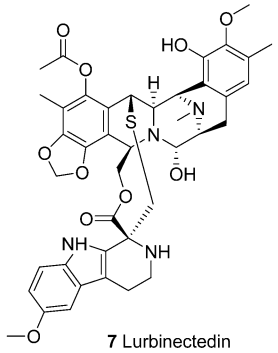
Chart 2



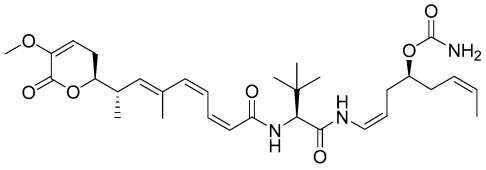
5 Kahalalide F



6 Zalypsis



7 Lurbinectedin



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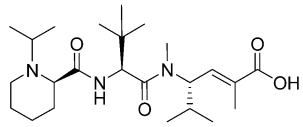
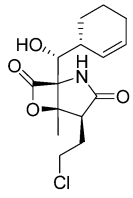


9 E-7974



10 Salinosporamide A

RESEARCH ADVANCES HERALD NEW PROMISE FOR OLD DRUGS AND DRUG LEADS

In preparing many reviews on the discovery and development of natural product drugs, several of which are cited above, as well as reading excellent reviews by others, the authors have been struck by the large number of potential drug leads that, for various reasons, have failed to advance to clinical and commercial use. Equally impressive, however, has been the progress in multidisciplinary natural product-related research that has been made in recent years and continues to be made at a rapid pace. This progress encompasses several important disciplinary areas.

Significant new bioactivities for "old" drugs have been identified through the discovery of new targets involved in the complex pathways leading to major diseases such as cancer, many of which have been identified through the use of natural product probes.[21,22] When new uses are found for "old" drugs that have been approved by regulatory agencies, such as the U.S. FDA and the European Medicines Agency (EMA), for commercialization and public use, the process is called drug repurposing, and the pros and cons of this approach have been reviewed and discussed.[23−27] This strategy offers promising opportunities for identifying new therapeutic applications for "old" drugs that already have been thoroughly assessed for clinical safety aspects related to toxicity and harmful side effects, thereby potentially reducing the costs of advanced preclinical and clinical development. There are, however, potential problems, such as the relevance of activity observed in a targeted screen, related to a particular disease and to the clinical efficacy in that disease, which may result in the performance of costly clinical trials that ultimately fail, as well as considerations of intellectual property rights and patent protection.[23,24] Such factors are important to pharmaceutical companies considering cost effectiveness when selecting candidates for further development.

The repurposing strategy has been adopted by the U.S. National Institutes of Health (NIH) through formation of the National Center for Advancing Translational Sciences (NCATS) (http://www.ncats.nih.gov/),[28] and a collection of approved and investigational agents, known as the NCATS Pharmaceutical Collection (NPC), is available as a publically accessible resource for high-throughput screening (http://

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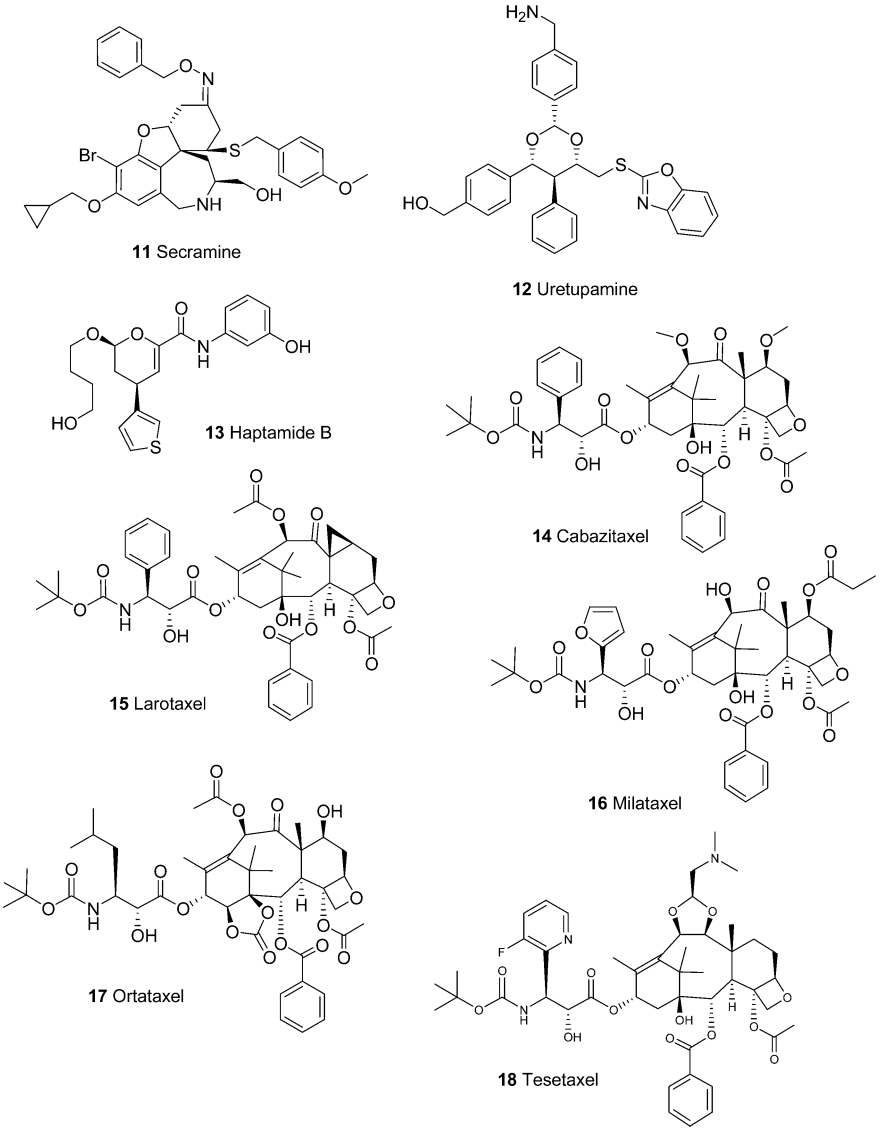
Chart 3



www.ncats.nih.gov/research/tools/preclinical/npc/pharmaceutical-collection.html). This collection "provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention". The drug repurposing strategy is being applied in several therapeutic areas.[29] These areas include the discovery of drugs for the treatment of Alzheimers disease;[30] cancer, including hematologic malignancies;[31−33] fungal diseases;[34,35] malaria;[36] and mycobacterial infections.[37,38] In all these areas, natural products have demonstrated significant activity, although synthetic agents were prevalent in the treatment of fungal diseases. Reference to http://www.drugrepurposing.info/ provides examples of over 1600 drug repurposing projects recorded in the patent and peer-reviewed literature (as of October 2013), and an outline of known drug repurposing projects that have yielded marketed or orphan-designated drugs may be found at http://www.drugrepurposing.info/index.php. Of the 52 drugs listed, 27 were naturally derived based on designation codes (N, ND, S*, and S*/NM) used by two of the authors in a recent review.[16]

Advances in microbial genomics and the detection and analysis of biosynthetic gene clusters encoding for polyketides (PKs), nonribosomal peptides (NRPs), and hybrid PK-NRP metabolites have led to the recognition that there are many more putative biosynthetic clusters present in long-studied microbes than originally deduced from conventional methods of fermentation and/or extraction. Increasing knowledge of the factors controlling the expression of these "cryptic clusters" will enable the isolation of potentially superior analogues of "old" drugs, as well as novel bioactive agents from long-studied and/or new microbial sources.[39−41] In addition, tools have been developed for engineering the biosynthesis of novel "non-natural" natural products through gene shuffling, domain deletions, and mutations,[42,43] and the application of these combinatorial biosynthetic techniques to the production of novel analogues of classes of anticancer agents, such as the anthracyclines, ansamycins, epothilones, enediynes, and aminocoumarins, has been reviewed.[44]

While natural products often exhibit highly potent and selective bioactivity, they underwent evolutionary selection to serve the needs of their producing organisms as opposed to serving as human therapeutics and, thus, have not been fine-tuned to possess the potency, selectivity, and pharmacokinetic properties desired in a clinically useful drug. Advances in total

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synthesis, medicinal chemistry, and combinatorial chemistry methodologies have led to the generation of pharmacologically improved analogues of original natural product leads and to environmentally and economically viable sources of drugs isolated in meager yields from their original natural sources.[5]

Adequate supply can be a serious limiting factor in the preclinical and clinical development of some naturally derived drugs, and the focus of many top synthetic groups on devising economically feasible synthetic strategies is a very welcome development for both clinicians conducting clinical trials and patient populations.

Identification of the pharmacophore, the arrangement of steric and electronic features necessary to ensure optimal interaction with a biological target and trigger or block its biological response, coupled with a versatile synthetic strategy allows for the "molecular editing" of unnecessary structural complexity. This approach, which involves the synthesis of an advanced intermediate that can be elaborated by different synthetic sequences to yield multiple analogues of varying complexity containing the common pharmacophore, has been described as "diverted total synthesis" (DTS).[45,46]

The synergy of combinatorial chemistry and natural products chemistry holds great potential for optimization of the known biological and pharmacokinetic properties of the parent natural product lead. It is also proving to be a potent tool for the discovery of analogues exhibiting biological activities beyond those previously associated with the parent natural product. Thus far, this strategy has performed remarkably well, yielding chemical probes such as secramine (**11**),[47] uretupamine (**12**),[48,49] and haptamide B (**13**).[50]

Biology-oriented synthesis (BIOS) expands on this basic concept by utilizing the structural information from natural products and their protein targets to focus on the most relevant chemical space for a particular target.[51−53] The scaffolds of natural products can be mapped in a hierarchical manner to create a scaffold tree that allows for logical pathways for the structural simplification of scaffolds. Proteins can be clustered by three-dimensional shape around the ligand binding sites, regardless of sequence similarity, into protein structure similarity clusters (PSSC).[54] The ligand of any member of a PSSC could be expected to exhibit some degree of complementarity toward other members of the PSSC and thus serve as a starting point for the development of modulators of the other members of the PSSC. BIOS represents a refinement of combinatorial libraries based on natural product scaffolds by focusing on the most biologically relevant chemical space for the target. Furthermore, it allows the transfer of knowledge about the modulation of a target by a natural product to a whole cluster of structurally related proteins, even when those proteins catalyze mechanistically different reactions.

Natural product drugs often have limited solubility in aqueous solvents and/or exhibit considerable cytotoxicity, resulting in narrow therapeutic indices, at least in the area of cancer chemotherapy. Advances in improving formulation and drug delivery methodology are addressing these liabilities, which frequently hinder the progress of natural products in preclinical and clinical studies. Strategies adopted include the synthesis of water-soluble prodrugs, which may include groups binding specifically to receptors on tumor cells, the preparation of polymer−drug complexes, which also may have the advantage of enhanced permeability and retention in tumors, the formation of nanoparticles, and the synthesis of antibody−drug conjugates, as referred to in the case of the marine-derived agent monomethyl auristatin E (**3**), mentioned in the Introduction,[17,55] as exemplified by the approval of Adcetris in 2011 by the U.S. FDA.[56]

■ REPURPOSING OF DRUGS AND DRUG LEADS

Given the authors' particular interests in cancer chemotherapy, many of the examples selected for brief discussion as repurposed drugs or drug leads in the following sections will be focused on this disease area. The examples given are by no means comprehensive, but are selected to illustrate the application of various advances, including modification of the base molecule via synthetic methods (which may include genetic modifications) in natural products research methodologies to aid in developing new and/or "improved" uses for "older" drugs or drug leads.

■ PLANT METABOLITES

As outlined in the Introduction, plants have historically been at the forefront of natural product drug discovery, and in the anticancer area, plant-derived agents, such as vinblastine and vincristine, etoposide, paclitaxel (Taxol), docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available. Nevertheless, as mentioned earlier, they all suffer from the liabilities of poor solubility in aqueous media and significant toxic side effects. Thus, there continues to be considerable research devoted to diminishing the impact of these factors, and numerous analogues and prodrugs of these agents have been synthesized and methods devised for increasing aqueous solubility and targeting specific tumors.[6,57,58]

Taxanes. Optimizing Efficacy and Delivery. The taxanes are considered one of the most important classes of cancer chemotherapeutic drugs in clinical use, and a comprehensive review of the ongoing research into the development of improved analogues and methods of delivery was recently published by Kingston.[59] Currently, the two most clinically effective drugs of this class are paclitaxel (Taxol) and docetaxel (Taxotere), which were approved by the U.S. FDA in 1993 and 1995, respectively. They continue to be extensively studied, and as of October 2013, reference to www.clinicaltrials.gov indicates that the number of clinical trials (active, completed, or recruiting) was 1748 for paclitaxel and 1533 for docetaxel, used either as single agents or in combination with other agents.

Many structural analogues have been synthesized that have improved (extended) activities, which can be considered a repurposing in one sense of a base active structure, and new formulations developed. Thus, the analogue cabazitaxel (**14**, Jevtana) was approved by the U.S. FDA in 2010 and is currently in 38 clinical trials, with seven completed (http://www.cancer.gov/drugdictionary?CdrID=53413), while the albumin-stabilized nanoparticle formulation of paclitaxel, Abraxane (nab-paclitaxel, ABI-007), is in 80 clinical trials, with 97 completed (http://www.cancer.gov/drugdictionary?CdrID=38690).

Other structural analogues in clinical trials are 7-DHA-taxol (7-docosahexaenoic acid conjugate, Taxoprexin; nine trials), larotaxel (**15**, RPR-109881A; eight trials), milataxel (**16**, MAC-321, TL139; three trials), ortataxel (**17**, BAY 59-8862; seven trials), tesetaxel (**18**, DJ-927, 14 trials), TPI-287 (**19**, 12 trials), and xyotax (CT-2103; paclitaxel polyglumex, an α-poly-L-

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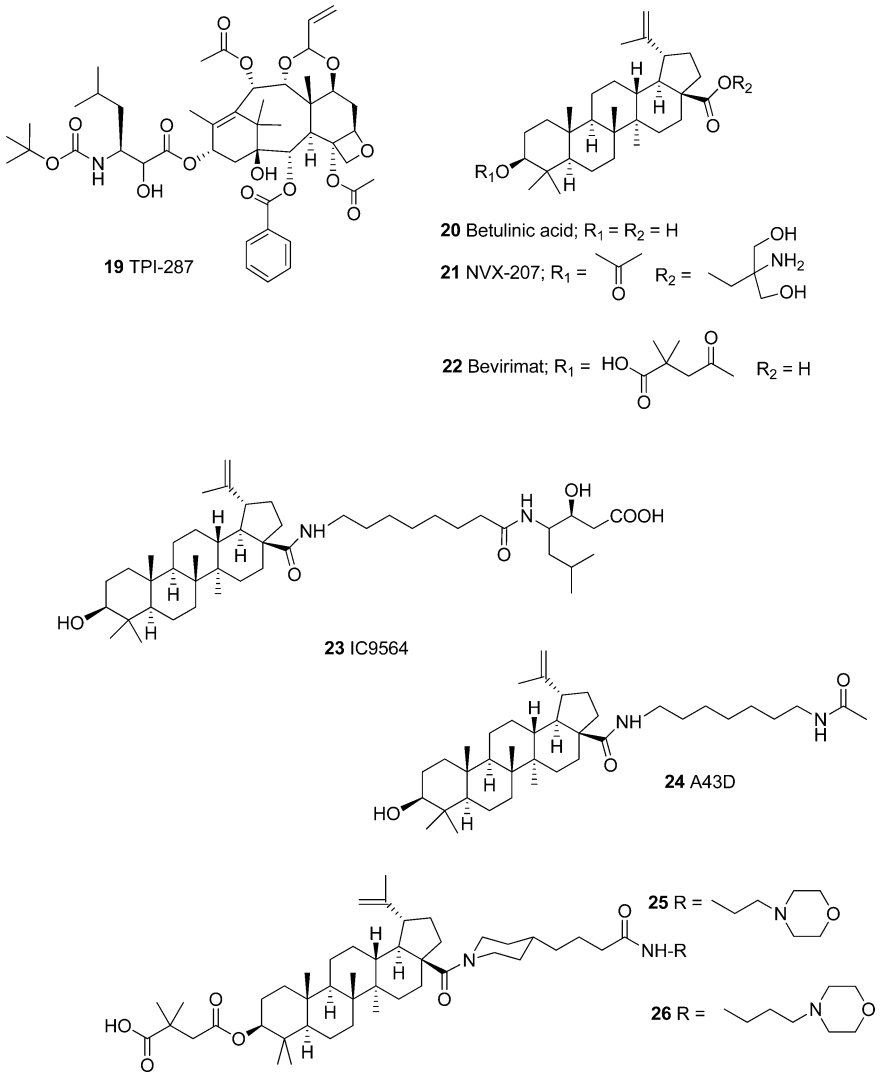
Chart 4



glutamic acid conjugate of paclitaxel; 24 trials). New formulations undergoing clinical trials include EndoTAG-1 (paclitaxel encapsulated in positively charged lipid-based complexes; four trials), Genexol-PM (paclitaxel loaded polymeric micelles; 13 trials), NK-105 (paclitaxel-incorporating micellar nanoparticles; one trial), and Tocosol (paclitaxel injectable vitamin E emulsion, S-8184; seven trials). In addition, clinical trials on four analogues have been discontinued and development has been terminated, but 23 taxanes remain in advanced preclinical development.[8]

Thus, despite the relative success of paclitaxel and docetaxel as clinical agents, advances in chemical methodologies, leading to potentially improved molecular entities based upon the original taxane backbone, and strategies for improved formulation and drug delivery continue to spur the quest for new versions of these "old" drugs that could be considered, in one sense, to be the results of a "repurposing by synthetic means" of the base molecule, but without involving the combinatorial or scaffold-hopping systems discussed later in this review.

Betulinic Acid. Cancer and AIDS. Betulinic acid (**20**) is a lupane-type triterpene with a long history, which has been isolated from many taxonomically diverse plant genera.[60] The birch tree, *Betula* spp., is a major source of both betulinic acid and its C_{28} alcohol precursor, betulin, of which the isolation was first reported in 1788. Betulinic acid has shown cytotoxicity against a range of cancer cell lines, and significant *in vivo* activity in human melanoma xenograft animal models led to the development of systemic and topical formulations of the agent for potential clinical trials. Observation of reduction of ultraviolet-C-induced DNA breakage in congenital melanocytic neval cells indicated a potential role as a chemopreventive agent,[61] and a 20% betulinic acid ointment is currently being evaluated in the treatment of dysplastic nevi (moderate to severe dysplasia; http://www.cancer.gov/drugdictionary?CdrID=496932). A novel semisynthetic derivative, NVX-207 (**21**), has shown significant in vivo activity in dogs with treatment-resistant malignancies and indicates that it may be a promising candidate for further clinical development.[62]

A range of biological activities, including antibacterial, anti-inflammatory, and antimalarial effects, have been reported for betulinic acid and several derivatives,[63] but the most important activities have been associated with inhibition of the replication of HIV strains. Several 3-*O*-succinyl derivatives have been synthesized and exhibit potent anti-HIV-1 activity,[64] and the 3,3′-dimethylsuccinyl derivative, named bevirimat (**22**), has completed four clinical trials (www.clinicaltrials.gov), including

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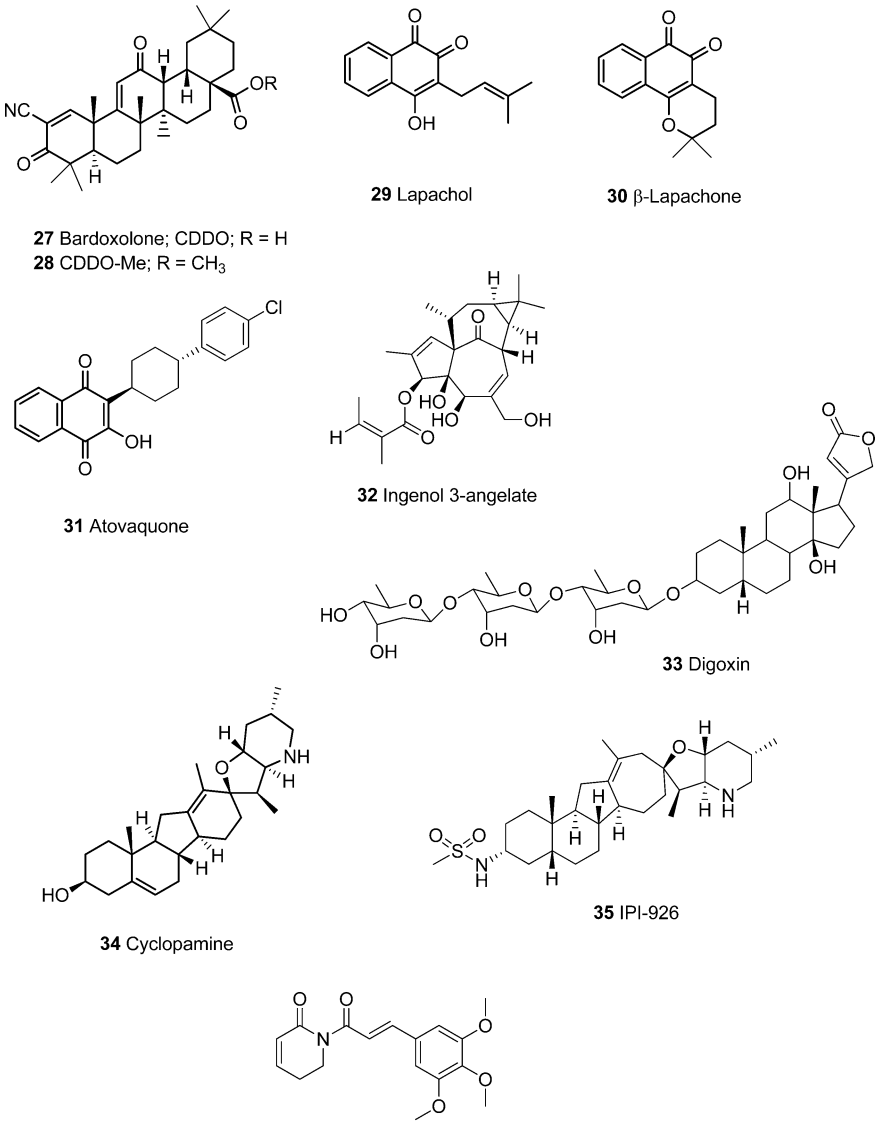
Chart 5



three phase II trials. Bevirimat represents a new class of HIV drugs called maturation inhibitors, and its novel mechanism of action offers potential for use either alone or in combination with current anti-AID agents.[65]

Due to the development of resistance attributed to naturally occurring polymorphisms in HIV-1 Gag, the further clinical development of bevirimat has been questioned,[66] but the synthesis of new derivatives overcoming such resistance in preclinical studies holds promise for development of other candidates for clinical trials.[67] In contrast to modification at the C-3 hydroxy group, derivatives with a side chain at C-28 block HIV-1 entry, and two entry inhibitors, IC9564 (**23**) and A43D (**24**), have been found to exhibit a broad spectrum of anti-HIV-1 activity.[68]

By combining both the C-3 and C-28 modifications, a derivative, A12-2, has been synthesized retaining both activities (inhibition of both entry and maturation) in the same molecule, with an IC_{50} value of 2.6 nM.[68] Analogues of A12-2 incorporating retention of both activities and showing greater stability to pooled human liver microsomes in in vitro studies (structures **25** and **26**) have been synthesized, and extensive structure−activity relationships have been published.[69] An excellent review on plant-derived triterpenoids as antitumor and anti-HIV agents providing more of the background information on this series of compounds has been published.[70] It will be interesting to follow the development of these agents as time progresses.

2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO; Bardoxolone). Cancer and Chronic Kidney Disease. Common triterpenoid acids, such as oleanolic and ursolic acid, exhibit weak anti-inflammatory and antitumor activities. Studies directed at the synthesis of new analogues having increased potencies yielded CDDO (**27**) and its methyl ester (**28**), which exhibit potent in vitro and in vivo antitumor activity against a wide range of tumors, including breast and pancreatic carcinomas and leukemias.[71] Significant activity shown by CDDO against epithelial ovarian carcinoma cell lines, including lines that were resistant to clinically used agents such as cisplatin, resulted in further evaluation of CDDO in the treatment of these cancers, which are leading causes of death

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from gynecologic cancers,[72] while evaluation of C-28 derivatives of CDDO, such as CDDO methyl ester (**55**, MeCDDO), CDDO imidazolide (CDDOIm), CDDO ethyl amide (CDDO-EA), CDDO trifluoroethyl amide (CDDO-TFEA), and CDDO diethylamide (CDDO-DE), against pediatric solid tumor cell lines indicated their potential for the treatment of high-risk pediatric solid tumors.[73]

Reported mechanistic effects include blocking of the synthesis of inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2), two enzymes involved in inflammation and carcinogenesis, and inhibition of the interleukin-1 (IL-1)-induced expression of the pro-inflammatory proteins matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-13 (MMP-13) (http://www.cancer.gov/drugdictionary?CdrID=453589). In vitro and in vivo studies of CDDO-Me have indicated that it has potent antiangiogenic activity.[74] Both CDDO and CDDO-Me (RTA-402; bardoxolone methyl) have been in phase I clinical trials against solid tumors and lymphomas and lymphoid malignancies, and RTA-402 did go into phase III trials in conjunction with Abbott and Reata for studies related to end stage renal disease. However, these trials were suspended due to serious adverse events, as were phase II trials for this indication in Japan following licensing to Kyowa Hakko Kirin.

Patients treated with CDDO-Me, however, showed significant improvement in their glomerular filtration rate (GFR) as measured by reduced serum creatinine levels, with the improvement being more pronounced in patients suffering from chronic kidney disease (CKD). CDDO-Me is an inducer of the Nrf2 [(nuclear factor (erythroid-derived 2)-like 2)] pathway, which can suppress oxidative stress and inflammation. Given these observed effects and the established role of oxidative stress and inflammation in CKD, especially in type 2 diabetes, a small study was performed to assess the clinical activity and safety of CDDO-Me in patients with moderate to severe CKD and type 2 diabetes, and an apparent increase in kidney function was observed.[75] A larger phase II trial in patients with advanced CKD and type 2 diabetes showed an improvement in the estimated GFR, which persisted at 52 weeks, suggesting that CDDO-Me may hold promise for the treatment of CKD.[76]

Following this publication, several concerns were expressed in letters to the editor of the journal as to whether the decrease in creatine levels reflected a real improvement in kidney function or may have been due to other factors, such as muscle wasting and significant weight loss observed with treated patients. A multinational, double-blind, placebo-controlled phase III trial was started in mid-2011 in patients with stage 4 CKD,[77] but as mentioned above, the trial was terminated in late 2012 because of adverse effects (http://www.clinicaltrials.gov/show/NCT01351675). Research aimed at overcoming the adverse effects and further developing this promising lead is anticipated, as mentioned by Abboud in a recent commentary.[78]

Lapachol and β-Lapachone. Cancer, Malaria, Babesiosis, and *Pneumocystis carinii* Pneumonia. Species of the genus *Tabebuia* have a history in the Amazonian region for the treatment of several diseases, including syphilis, fever, malaria, cutaneous infections, and stomach disorders. Claims in the 1960s for clinical efficacy in the treatment of cancers, particularly in Brazil, led to widespread sales of the bark and trunk wood of several species [*T. impetiginosa* (syn *T. avellanedae*), *T. rosea*, and *T. serratifolia*] under various names such as "pau d'arco" or "lapacho". Of the many bioactive compounds isolated, the naphthaquinones lapachol (**29**), first isolated in 1882 from *T. avellanedae*, and β-lapachone (**30**) have been the most studied.

Observation of significant in vivo antitumor activity for lapachol in some early mouse models resulted in its advancement to clinical trials by the NCI in the 1970s, but the trials were terminated due to unacceptable levels of toxicity.[79] Interest in β-lapachone (ARQ 501; http://www.cancer.gov/drugdictionary?CdrID=357565) was prompted by its activity against a range of tumor cell lines, including breast, leukemia, and prostate lines and several multidrug-resistant lines.[80] Developed by ArQule under the code name ARQ 501, it had completed six clinical trials (as of October 2013) against a range of solid tumors, including pancreatic cancer, in combination with gemcitabine. An important variation, the water-soluble prodrug ARQ 761 (http://www.cancer.gov/drugdictionary?CdrID=715599), is now entering a phase I trial against advanced solid tumors.

Lapachol, which was used for the treatment of malaria in the late 19th century, formed the model (i.e., repurposing of a base active structure) for the synthesis of atovaquone (**31**), which, in combination with proguanil hydrochloride, has proved effective in the treatment of malaria and is available in many countries under the trade name Malarone for treatment of acute, uncomplicated malaria caused by *Plasmodium falciparum*;[81] as of October 2013, there are 14 clinical studies either recently completed or in progress (www.clinicaltrials.gov). Some cases of resistance have been reported.[82] Atovaquone has also been shown to be effective for the treatment of mild and moderate *P. carinii* pneumonia[83] and, in combination with azithromycin, for the treatment of babesiosis, caused by *Babesia microti*, a tick-borne, malaria-like infection that may cause severe illness and death and which is enzootic mainly in southern New England, southern New York, Wisconsin, and Minnesota.[84]

Ingenyl-3-angelate (PEP005; Ingenol Metbutate; Picato). Carcinogenicity or Anticancer. The latices of plants of the Euphorbiaceae family, particularly members of the *Euphorbia* genus, have long been known to possess irritant and carcinogenic properties, and these properties have been associated with diterpenes of the phorbol and ingenane classes.[85] The sap of *Euphorbia peplus* was reported to be used in Australia as a "folk treatment" for skin cancers.[86] The active agent of this sap was identified as ingenol-3-angelate (**32**),[87] and topical applications of this compound, also known as PEP005, showed significant in vivo activity against a series of subcutaneous mouse and human tumors in mice. It also had potent antileukemic effects in addition to its topical effects,[88] and its mechanism of action was identified as a PKC activator. In another study, PEP005 showed differential effects on PKCα and PKCδ, suggesting that the drug induced apoptosis through this pathway and that targeting PKC isoforms is a valid approach to cancer therapy.[89]

As of October 2013, a topical formulation of the compound had completed two phase III trials for the treatment of actinic keratosis, and four more trials were in progress;[90] in addition, four phase II trials for the treatment of basal cell carcinoma had been completed (http://www.cancer.gov/drugdictionary?CdrID=432941). A gel formulation of the drug was approved in 2012 by the FDA and the EMA for the treatment of actinic keratosis.

Digoxin and Related Cardiac Glycosides. Heart Failure to Cancer. Digoxin (**33**) and related cardiac glycosides such as

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digitoxin and ouabain have long been known for their efficacy in treatment of congestive heart failure and as antiarrhythmic agents.[91] Recent research, showing their effects on mechanisms involving cell-signal transduction resulting in selective control of the proliferation of human tumors compared to normal cells, has demonstrated a new role for these compounds in the area of cancer therapy.[7,92]

In a repurposing study involving the testing of over 3000 compounds in an in vitro prostate cancer cell line screen, digoxin emerged as the leading candidate with a mean IC_{50} of 163 nM, and evaluation of its use by over 47 000 men over a 20-year period from 1986 to 2006 showed that it was associated with a 25% lower prostate cancer risk compared to nonusers.[93] These observations amply justify further preclinical and clinical development of digoxin as a drug for the treatment of prostate cancer. As of October 2013, one phase II trial for recurrent prostate cancer had been completed (http://www.cancer.gov/drugdictionary?CdrID=485249).

Digoxin binds to estrogen receptors, and its use has been associated with increased incidence of breast and uterine cancers where the cancers are estrogen receptive (ER).[94] When drug use is terminated, the cancer incidence rapidly reverts to that of nonusers, thus paralleling the patterns of estrogen and suggesting that the digoxin acts through ER stimulation of ductal/acinar cell proliferation, thereby accelerating the growth of nascent cancers. Overall, however, the risk of breast cancer relapse in digoxin users was not increased significantly, although risks of recurrence were greater for users having ER + tumors during the first year following diagnosis.[95] For women having ovarian and cervical cancers that are relatively estrogen-insensitive, the incidence of the cancers is unaffected.[95]

As of October 2013, two phase II trials were in progress, with one being in patients with newly diagnosed operable breast cancer and the other in patients with metastatic breast cancer, in combination with capecitabine (http://www.cancer.gov/drugdictionary?CdrID=485249). In addition, it is interesting to note that, in 2001, digitoxin received FDA orphan drug designation for the treatment of ovarian cancer and soft tissue sarcomas (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm).

Cyclopamine. From Teratogen to Potential Anticancer Agents. In the 1950s, sheepherders in Idaho observed that consumption of *Veratrum californicum* by pregnant sheep was associated with birth defects in lambs, including cyclopia in severe cases. These teratogenic effects have been attributed to the presence of alkaloids of the jervine class, particularly cyclopamine (**34**), which specifically inhibit vertebrate cellular responses to the hedgehog family of secreted growth factors.[96−99] The hedgehog cell signaling pathway normally is quiescent in adult cells, but aberrant activation of the pathway in adults has been implicated in many cancers, including cancers of the pancreas, prostate, lung (small cell), and brain (glioma).[100−102] Activation of this pathway is blocked by cyclopamine, and analogues and prodrugs are in various stages of preclinical and clinical development.[103−106]

A novel, semisynthetic, and orally active analogue of cyclopamine, IPI-926 (**35**, Saridegib), having greatly improved pharmaceutical properties and potency, has been developed[107] (http://www.cancer.gov/drugdictionary?cdrid=616875), and five clinical trials have been completed. These include phase I trials in patients with advanced and/or metastatic solid tumor malignancies[108] and in combination with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) for advanced pancreatic adenocarcinoma, as well as phase II trials in patients with metastatic or locally advanced (unresectable) chondrosarcomas and, in combination with gemcitabine, for metastatic pancreatic cancer (http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=7477483).

As of October 2013, a pilot study of IPI-926 in combination with cetuximab was active in recurrent head and neck cancer (http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=7729775). An interesting development has been the design and synthesis of an HPMA [(*N*-(2-hydroxypropyl) methacrylamide)] copolymer−cyclopamine conjugate as a macromolecular therapeutic having improved drug solubility and decreased systemic toxicity.[109] Like free cyclopamine, it showed a selective inhibitory effect on prostate cancer stem cells (CSCs) in relation to bulk cancer cells in an in vitro prostate cancer model. In contrast, docetaxel, a traditional chemotherapeutic agent for prostate cancer, showed preferential cytotoxicity to the bulk cancer cells.[109] These results suggested a potential treatment involving a combination of macromolecular therapeutics targeting both bulk prostate tumor cells and CSCs.

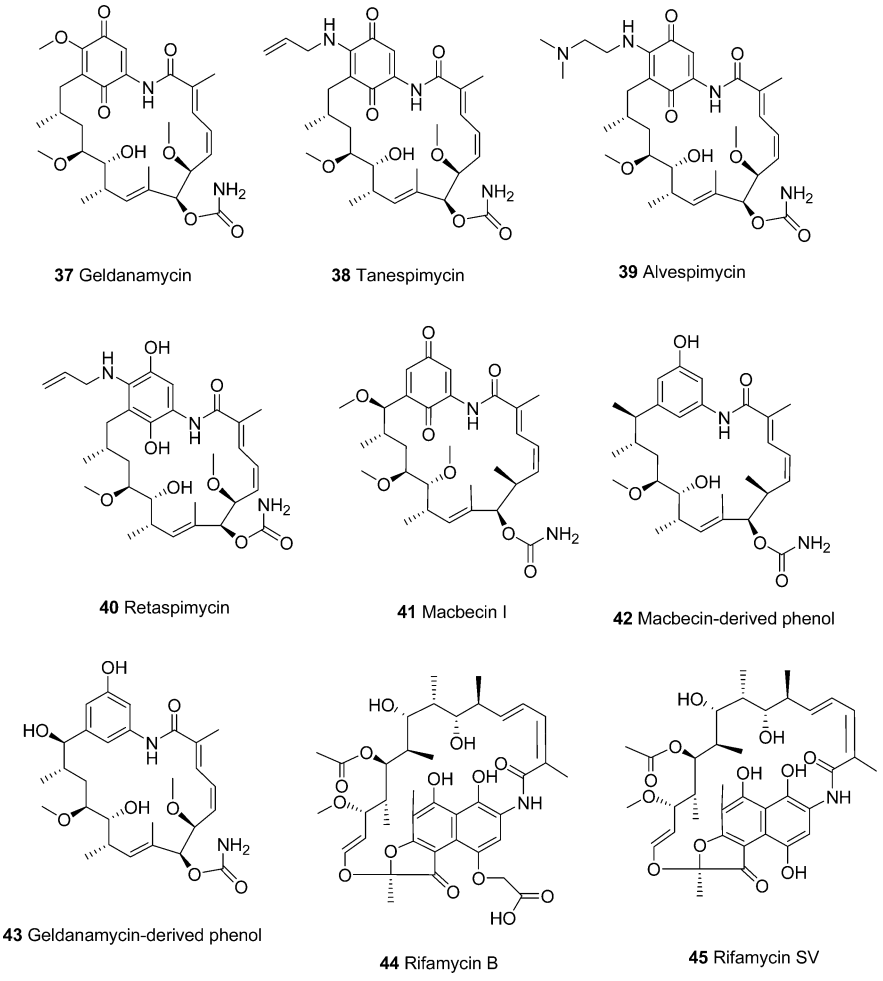
To this end, a combination macromolecular therapy containing two drug conjugates, HPMA copolymer−cyclopamine conjugate (P-CYP) and HPMA copolymer−docetaxel conjugate (P-DTX), has been developed and has been shown to be highly effective both in vitro and in vivo in a PC-3 xenograft mouse model.[110] In addition, preclinical studies indicate that cyclopamine may be effective in the treatment of psoriasis,[111] though it has been reported that the hedgehog (Hh) pathway is not activated in psoriasis, and the proposed use of Hh antagonists as antipsoriatic agents has been questioned.[112]

Piperlongumine (Piplartine). Focus on Cancer. The isolation of piperlongumine, also known as piplartine, from *Piper longum* was first reported in 1961.[113] The plant is used extensively in Ayurvedic medicine and is reported to have a wide range of pharmacological effects, including cytotoxicity and antidepressant, antiatherosclerotic, antidiabetic, antibacterial, antifungal, leishmanicidal, trypanocidal, and schistosomicidal activities.[113] The most promise related to potential drug development, however, has been shown in the cancer area, where it has shown selective activity against 14 cancer cell lines of different origin, but is inactive in six normal cell lines; in addition, it exhibits significant antitumor effects in mouse xenograft tumor models representing melanoma, bladder, breast, and lung cancers, with no apparent toxicity being observed in normal mice.[114]

On the basis of detailed mechanistic studies, it has been proposed that piperlongumine acts by selectively increasing the level of reactive oxygen species (ROS) in cancer cells, possibly through effects on stress response enzymes, such as glutathione-*S*-transferase P 1 (GSTP1) and carbonyl reductase (CBR1), which are both known to detoxify xenobiotics.[114,115] Subsequently, it has been reported that piperlongumine is an inhibitor of the ubiquitin-proteasome system, raising the possibility that its induction of ROS may be associated with proteasome inhibition.[116] Piperlongumine has also been reported to induce rapid depletion of the androgen receptor in prostate cancer cell lines, suggesting possible applications in both the prevention and treatment of prostate cancers.[117]

Synthetic and structure activity studies have yielded 80 piperlongumine analogues, which demonstrate structural modifications that retain, enhance, and diminish key

Chart 6



piperlongumine-associated effects on cells, including elevation of ROS and cancer cell death.[118] In some cell lines, analogues lacking the 7,8-double bond showed elevated ROS levels but significantly diminished cell death relative to piperlongumine, indicating that, in these cases, oxidative stress appears to be insufficient to induce cell death; it was suggested that in these cases the cellular toxicity exerted by piperlongumine might be more the result of elevation of protein glutathionylation or other cellular cross-linking events. It seems clear that piperlongumine and its analogues hold great promise for the development of novel and more effective anticancer agents.

MICROBIAL METABOLITES

Geldanamycin and Analogues. Cancer and Infectious Diseases. The benzoquinone ansamycin antibiotic geldanamycin (**37**), isolated from *Streptomyces hygroscopicus* var. *geldanus*, was first reported in 1970[119] and shown to have antiparasitic activity. Later studies demonstrated antitumor activity, and in 1994 it was shown to bind to heat shock protein 90 (Hsp90);[120] three years later, it was reported to bind specifically to an ATP site at the N-terminus end of Hsp90, altering its chaperone activity and indirectly leading to cell death.[121]

The history of the various structural modifications of geldanamycin leading up to the initial development of the clinical candidates tanespimycin (**38**, 17-AAG; http://www.cancer.gov/drugdictionary?CdrID=43635) and alvespimycin (**39**, 17-DMAG; http://www.cancer.gov/drugdictionary?CdrID=378203) has been reviewed,[122,123] and, as of October 2013, tanespimycin and alvespimycin, as its hydrochloride salt, had completed 27 and five clinical trials, respectively. Reduction of tanespimycin gives the hydroquinone retaspimycin (**40**, IPI-504; http://www.cancer.gov/drugdictionary?CdrID=437784), which formed a more stable hydrochloride salt; retaspimycin has completed six clinical trials and is in an active trial against KRAS mutant non-small-cell lung cancer in combination with the rapamycin analogue everolimus.[124]

Macbecin (**41**), a close relative of geldanamycin, has also been reported to be an Hsp90 inhibitor, which exhibits both in vitro and in vivo activity in mice and which is more water-soluble and less toxic than the geldanamycin derivatives that have been in recent trials.[125] Genetic modification of the macbecin biosynthetic complex in *Actinosynnema pretiosum* ssp. *pretiosum* yielded macbecin-based molecules, including one in which the quinone moiety is replaced by a phenol (**42**). This product demonstrated similar in vitro and in vivo activity to that shown by tanespimycin, but it bound more tightly to Hsp90 and was active at a lower molar dose in both cellular and murine assays.[126] A similar phenolic analogue (**43**) was produced using the geldanamycin producer *S. hygroscopicus*,[127] while other geldanamycin analogues have been reported from genetically engineered strains of *S. hygroscopicus* JCM4427.[128]

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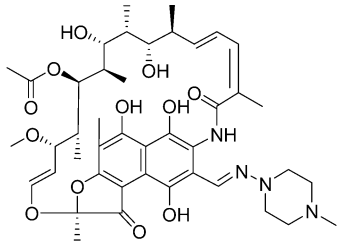
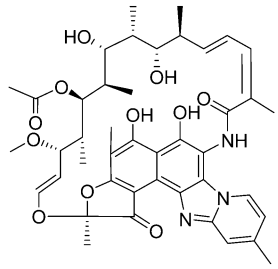
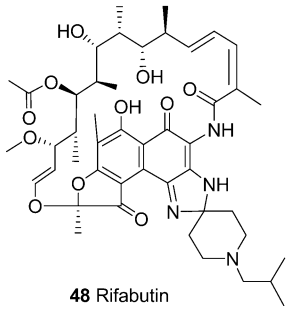
Chart 7



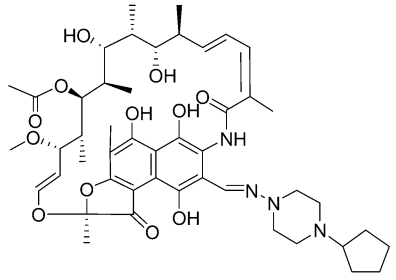
46 Rifampicin



47 Rifamixin



48 Rifabutin



49 Rifapentine

Thus, different modified ansamycin macrocycles with Hsp90 activity are available for future screening.

Of added interest is the fact that Hsp90 is also an important stress protein utilized by parasitic microbes, and evidence demonstrating its key role in the growth of pathogenic organisms, such as *Candida albicans*, *Plasmodium falciparum*, *Giardia lamblia*, *Trypanosoma cruzi*, and *Leishmania donovani*, is mounting.[129] Thus, geldanamycin and analogues such as tanespimycin have shown in vitro and in vivo activity against *P. falciparum*, *P. berghei*, *T. evansi*, and *T. brucei*,[129] and further research into the development of these and other ansamycin antibiotics as anti-infective agents seems merited. It is, however, somewhat ironic that the original isolation of geldanamycin was by following its activity against the parasite *Tetrahymena pyriformis* in vitro and demonstrated oral in vivo activity against the parasite *Syphacia oblevata*.

Rifamycins. Tuberculosis and MDR *Acinetobacter baumanii*. Rifamycins were first discovered in 1957 as a complex antibacterial mixture of several compounds isolated from an actinomycete that was originally classified as *Streptomyces mediterranei*,[130] reclassified as *Nocardia mediterranea* in 1969, and finally designated in 1986 as *Amycolatopsis mediterranei*, a newly defined genus.[131] The only product isolated in pure crystalline form from the mixture as a minor component was rifamycin B (**44**). The base molecule in this series, rifamycin SV (**45**), which is a biosynthetic precursor to rifamycin B, was launched in the mid-1960s as an antimycobacterial (tuberculosis) agent. During the following five decades, well over 300 variations on the structure have been reported as being biologically evaluated, ranging from in vitro testing through clinical trials to becoming approved drugs.

A search of the Thomson-Reuters Integrity database in October 2013 showed 178 different compounds of similar structure listed, with seven being shown as approved. Comparison of the various rifamycins is given in a review of bacterial RNA polymerase inhibitors.[131] Since the launch of rifamycin SV, four other analogues have been approved by the U.S. FDA or equivalent organizations, namely, rifampicin in 1967 (**46**), rifamixin in 1988 (**47**), rifabutin (**48**) in 1992, and rifapentine (**49**) in 1998. As of October 2013, there appear to be no rifamycin-like molecules in clinical trials for treatment of mycobacterial infections, though a recent publication in the infectious disease literature implies that increased doses of these agents, in conjunction with other antituberculosis drugs, are still viable treatments.[132]

Of particular note is the report in August 2012 that three rifamycins, rifampicin, rifamyxin, and rifabutine, have been found to be effective in preventing the growth and cellular respiration of multidrug-resistant (MDR) *Acinetobacter baumanii* (MDRAb), which is an important pathogen associated with wound infections afflicting U.S. military personnel.[133] The authors screened 450 FDA-approved agents obtained from the NIH Clinical Collection against eight strains of bacteria of concern to public health and the biodefense community, as well as 12 MDR clinical samples of *A. baumanii* isolated from combatants wounded in Iraq and Afghanistan. Activities were assessed using assays having growth inhibition and cellular respiration end points. Of the 450 compounds tested, 19 inhibited pathogen growth at a relatively high concentration of approximately 100 μM, but the three rifamycin analogues proved to be the most effective at lower concentrations.

As noted by the authors, "this single class of antimicrobials appears to have broad-spectrum antimicrobial activity that includes select agent surrogates of MDRAb." Thus, the rifamycins hold significant potential as antimicrobial agents for the treatment of nosocomial infections caused by MDRAb present in military hospitals, as well as for treating infections caused by possible biothreat agents.

Rapamycins. Molecules for Many Diseases. The discovery of rapamycin (**50a**), a 31-membered macrocyclic antibiotic produced by the fermentation of a strain of *Streptomyces hygroscopicus* isolated from soil samples in Rapa Nui (Easter Island), was first reported in 1975.[134−136] While first reported to have antifungal activity, rapamycin was unsuccessful as an antifungal agent due to its immunosuppressant effects. Initial reports of antitumor activity in 1984

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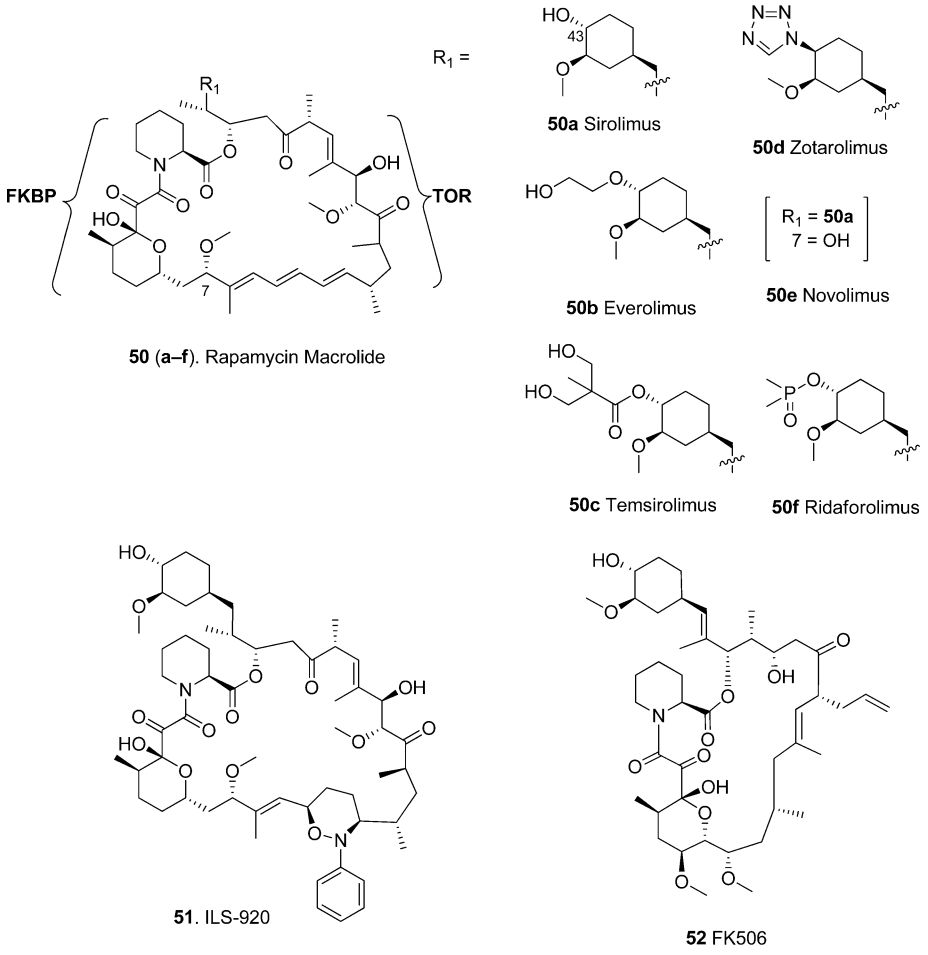
Chart 8



were not pursued, but reports of the identification of TOR ("target of Rapamycin") as the molecular target in yeast in 1991,[137] followed by mTOR as the mammalian homologue in 1994,[138] ultimately led to the development of a wide variety of anticancer and other pharmacologic agents. In 1999, rapamycin (sirolimus) was approved by the U.S. FDA as an immunosuppressive agent. Chemical modifications yielded two clinically approved anticancer drugs, everolimus (**50b**, Afinitor) and temsirolimus (**50c**, Torisel), and zotarolimus (**50d**) as a component of stents for restenosis.[139,140] As of October 2013, sirolimus had completed 60 clinical trials and is currently in 56 phase I/II trials for the treatment of various cancers (http://www.cancer.gov/drugdictionary?CdrID=42555). Everolimus (Afinitor) was initially launched in 2004 as an immunosuppressive agent, and then in 2009, 2010, 2011, and 2012, the compound was approved for the treatment of kidney, brain, pancreatic, and breast cancers, respectively. It is currently in 164 clinical trials, having completed 165 trials (http://www.cancer.gov/drugdictionary?CdrID=372905). In addition, in 2012, it was released to be used as a stent in the treatment of coronary and peripheral arterial diseases in the U.S. Temsirolimus (Torisel; CCI-779) was approved as a treatment for renal carcinoma in the U.S. in 2007 and is active in 53 clinical trials, having completed 103 trials (http://www.cancer.gov/drugdictionary?CdrID=43369). Zotarolimus (**50d**) became available in the U.S. in 2005 for the treatment of arterial restenosis (as a component of a stent), and recently the EU approved a stent containing novolimus (**50e**), a metabolite of rapamycin where the 7-methoxy group is demethylated to give a hydroxy moiety.

Another rapamycin derivative showing promise in the treatment of cancer is ridaforolimus (**50f**, AP-23573), which has completed 30 clinical trials, including phase III trials for the treatment of soft tissue carcinoma (NCT00538239) and bone cancer (NCT00538239), and it is active in an early trial in combination with paclitaxel and carboplatin for the treatment of patients with advanced or recurrent solid tumors (http://www.cancer.gov/drugdictionary?CdrID=354223). However, it was withdrawn by Merck for bone cancer and went into phase II trials for non-small-cell lung cancer with the *Kras* mutation under the aegis of Ariad Phaarmaceuticals, though this trial is now quoted as being "terminated" but without a listed reason (NCT00818675); an extension safety trial is still ongoing but without a phase listed (NCT00836927). Currently, a prodrug of rapamycin, ABI-009 (a nanoparticle-encapsulated formulation), is in phase I clinical trials for the treatment of solid tumors (http://clinicaltrials.gov/show/NCT00635284).

Modification of the triene portion of the rapamycin macrocyclic ring affords neuroprotective analogues lacking immunosuppressive activity,[140] and one product, ILS-920 (**51**), was under development for treating stroke,[141] with a phase I clinical trial for the treatment of acute ischemic stroke completed (http://clinicaltrials.gov/show/NCT00827190). Furthermore, a report on the possibility of rapamycin plus lithium aiding in the treatment of Huntington's disease was published in 2008.[142]

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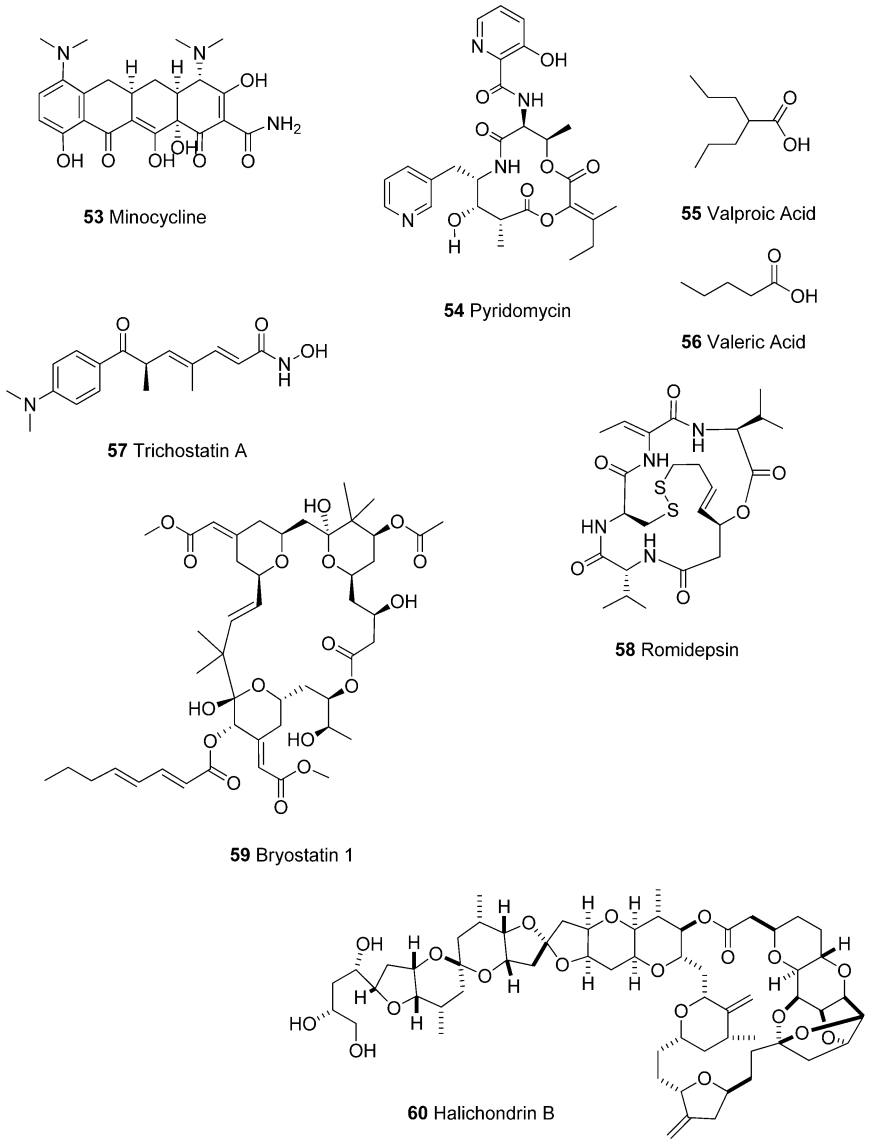
Chart 9



FK506 (**52**), a microbial compound with a close similarity to rapamycin, originally discovered in 1984, was approved as an immunosuppressant in Japan in 1993 and a year later in the U.S. as a treatment for kidney and liver transplant rejection. Over the next 15−20 years it has been approved for treatment of a large number of immunological related diseases and is currently active in over 100 clinical trials, including phase III trials in acute myeloid leukemia, in particular in graft versus host disease in patients who have undergone bone-marrow transplants (http://www.cancer.gov/drugdictionary?CdrlD=42009).

In an entirely different disease area, quite reminiscent of the original discovery of rapamycin, FK506 has shown activity against *Exerohilum rostratum*, one of the major pathogens involved in the outbreak of fungal meningitis and other infections in 2013 associated with contaminated compounding solutions.[143] These observations clearly indicate that this basic macrocyclic structure may well advance into areas not envisioned in earlier days.

The potential for producing novel biologically active analogues of rapamycin (so-called "rapalogs") through the genetic manipulation of biosynthetic pathways has been extensively studied, with a focus on precursor-directed biosynthesis, genetic manipulation, and mutasynthesis.[140,144,145] These papers demonstrate the multiplicity of materials that can be produced by modification of biosynthetic units and illustrate the problems involved in the regulation of any biosynthetic process, particularly related to mutasynthetic processes designed to increase yields of desired molecules. The potential of these processes in developing bioengineered strains for producing novel rapalogs and for utilizing the products for biosynthetic medicinal chemistry is discussed in recent reviews.[146,147]

Thus, rapamycin and its close chemical relatives can almost be called "a molecule for many diseases" since the rapamycins (and FK506) now cover molecules that have biological properties ranging from initial antifungal activities through immunomodulation to antitumor therapies, and even to use in stents to avoid plaque formation in the blood circulation, with added potential as treatments for Huntington's and serious microbial infections.

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Minocycline. Antimicrobial to Stroke. Minocycline (**53**) can be considered to be a second-generation tetracycline and was first used as an antibiotic in 1971. Over the years, this antibiotic was found to have multiple activities including anti-inflammatory action in double-blind studies in rheumatoid arthritis.[148] Since then, a variety of other areas have been looked at, with its potential for use as an adjuvant in stroke being of significant import.[149] Tissue plasminogen activator (tPA) is the only approved treatment for stroke, but it has both a time limit of about three hours after stroke for use and also is not effective in a fair number of cases. Clinical trials of minocycline in stroke were started,[150] with a report on the first phase I and II trials on dose levels and safety being published in 2010.[151]

Further studies at the phase I/II level are now undergoing patient recruitment, looking at effects of minocycline in intracerebral hemorrhage patients under the designation NCT01805895. There was one phase IV trial looking at neuroprotection reported under NCT00930020 in Singapore that was terminated, but no details have yet been published. Thus it appears from the literature that there may well be positive effects from minocycline treatment in some ischemic episodes, and it will be interesting to see if the original thesis with respect to adding this agent to tPA treatment will be successful.[150] If it is, then this may well aid in the immediate treatment of stroke.

Pyridomycin. Revival of a Long-Neglected Anti-TB Agent. The isolation of pyridomycin (**54**) from *Streptomyces pyridomyceticus* was first reported in 1953[152] and later was also shown to be produced by *Dactylosporangium fulvum*.[153] Pyridomycin exhibited specific activity against several mycobacteria, including *M. tuberculosis* and *M. smegmatis*, but was not further developed, possibly because the synthetic antimycobacterial drug isoniazid was also discovered in the early 1950s. At that time, the drug of choice for treating tuberculosis was streptomycin, but development of resistance to this agent promoted a search for alternative drugs, and isoniazid was found to be effective in overcoming the resistance.

A major challenge in controlling tuberculosis is the ability of *M. tuberculosis* to remain dormant within human macrophages, and this has necessitated the use of multidrug therapy usually involving regimens of four or more drugs taken for periods of six to 12 months.[154] Over the past decade, strains of *M. tuberculosis* have emerged giving rise to multidrug-resistance to isoniazid and rifampin, extensive drug-resistance to regimens using multiple drugs [e.g., isoniazid, the rifamycins (rifampicin, rifabutin, and rifapentine), aminoglycosides (streptomycin, amikacin, and kanamycin), and the peptide antibiotic (capreomycin)], and more recently total drug-resistance, where all available drugs are ineffective.[154,155]

Isoniazid inhibits the fatty acid synthesis enzyme enoyl-acyl-carrier-protein reductase (*Inh*A), thereby blocking the synthesis of mycolic acids that are key protective components of the cell wall of *M. tuberculosis*, but it first requires activation by an intracellular enzyme called KatG before it can bind to *Inh*A. Resistance to isoniazid has developed as the result of mutations in *M. tuberculosis* that occur in the *Kat*G gene. Pyridomycin has been found to act by the same mechanism as isoniazid, but it binds directly to *Inh*A, thereby circumventing the key isoniazid resistance mechanism.[156] Indeed, Hartkoorn et al. note that "no cross resistance was observed between pyridomycin and isoniazid, both in laboratory strains containing mutations in *Inh*A, or in the most frequently encountered isoniazid-resistant clinical isolates that contain mutations in *Kat*G". Furthermore, pyridomycin has the added advantage in that it also kills *M. tuberculosis* within macrophages, which as noted above, is a major challenge in controlling tuberculosis.[154−156]

The cloning and identification of the biosynthetic gene cluster for pyridomycin from *Streptomyces pyridomyceticus* has recently been reported, offering a biosynthetic route to the production of analogues for structure−activity studies and the possibility of generating more effective candidates for advanced development.[157] Thus, pyridomycin affords a highly promising lead molecule for the development of more effective drugs for the treatment of a disease that has once more emerged as a global health emergency.

Histone Deacetylase Inhibitors. Valproic Acid and Microbial Natural Products as Potential Treatments for Endometriosis. Endometriosis is a puzzling gynecological condition responsible for significant disabilities in women of reproductive age.[158] Though there are drug candidates in clinical trials, with more than 140 trials shown in the clinical trials database (www.clinicaltrials.gov), none have yet made it to final approval by the FDA.

Over the past decade, evidence has been amassed that indicates that endometriosis may be an epigenetic disease. Although in a number of cases the evidence is circumstantial, overall a reasonable case can be made for this proposal. Thus, in baboon models of endometriosis, the *HOXA10* promoter was shown to be hypermethylated,[159] and, in comparable mouse models, there was down-regulation of *HOXA10* gene expression as well as hypermethylation of the promoter.[160] In women with endometriosis, this gene is significantly reduced in their endometrial tissue, possibly due to the known gene-silencing effect of hypermethylated promoters.[161]

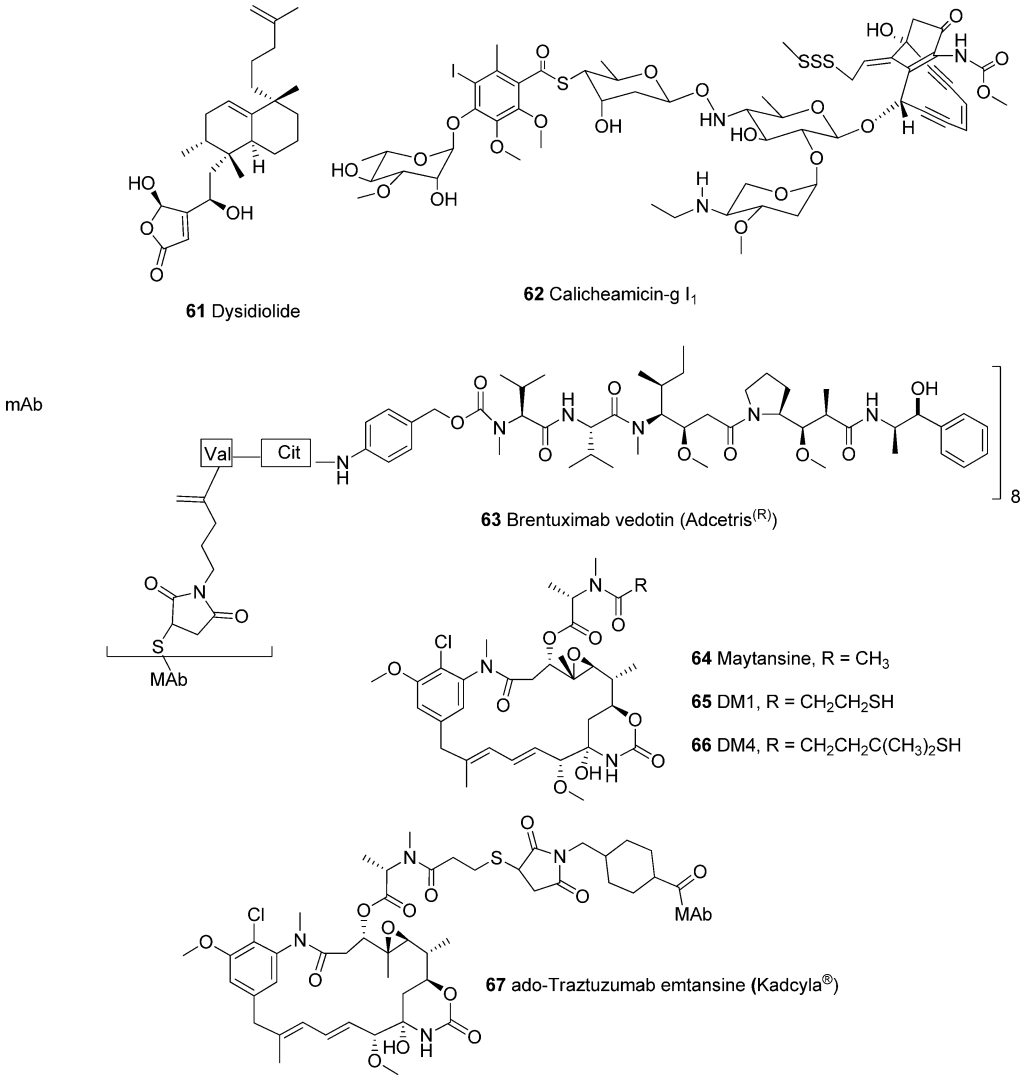
Valproic acid (**55**), which was first synthesized in 1882 as an analogue of valeric acid (**56**) isolated from *Valeriana officinalis*, was thought for many decades to be metabolically inert and was used as a solvent. Its anticonvulsant properties were discovered by accident when being used as a solvent for other compounds being tested for anticonvulsant activity, and it was approved by the FDA in 1978 for the treatment of epilepsy.[162] Nowadays it is also used as an HDAC inhibitor,[163] together with one of the prototypic HDAC inhibitors, the fungal product trichostatin A (**57**).[164] Both of these agents significantly altered the expression of a variety of gene products in endometrial cells and in animal models of endometriosis (see Table 2 in ref 161), and thus a case can be made for the repurposing of valproic acid, which although not a natural product, mimics the activity of natural products on HDACs.

On the other hand, the table referred to above lists a whole range of HDAC inhibitors, including the recently approved natural product romidepsin (**58**, FK228) and other natural products such as apicidin and TSA, which also alter gene products or genes in cells from endometriotic lesions and thus may be candidates in due course for repurposing. Thus, although valproic acid may be the first to be utilized and is not a natural product, though based upon one, it may well prove that these other natural product HDAC inhibitors that affect different isotypes of the protein may well follow on as candidates for repurposing for this debilitating disease of premenopausal women.

■ MARINE METABOLITES

Bryostatin and Bryologs. Cancer, Alzheimer's Disease, and HIV. The bryostatins are a class of highly oxygenated

Chart 10



macrolides, shown to have signal transduction activities resulting from targeting of protein kinase C (PKC). A more than three decade long effort that culminated in the isolation and purification of 20 bryostatin structures has been well documented by a variety of authors over the years.[165−173]

Bryostatin 1 (**59**), which was the most abundant of the group and had been isolated and purified to cGMP quality mainly by workers at the NCI-Frederick in the late 1980s, has been the focus of preclinical and clinical studies. This compound went into more than 80 clinical trials (at phases I and II) both as a single agent and in conjunction with cytotoxins. However, to date, only a few patients showed responses to the agent. Details on the clinical trials of bryostatin 1 have been recently reviewed.[173]

Currently, there are no cancer clinical trials listed as of October 2013 that are still active; however, the base molecule is now being investigated as a potential treatment for Alzheimer's disease,[174−178] with a phase I trial approved in 2008 under the sponsorship of the Blanchette Rockefeller Neurosciences Institute in West Virginia. The current status of this trial is listed as "unknown" on www.clinicaltrials.gov.

The bryostatins have been an attractive synthetic target, and several reports and reviews have been published detailing their chemistry.[169,171,172,179−182] None of these methods, however, are viable for the large-scale production of any of the bryostatins for further development.

On the basis of their model of the binding site of the phorbol esters on PKC, the Wender group has developed a class of simpler bryostatin analogues, known colloquially as "bryologs", that maintain the putative binding sites at the oxygen atoms at C_1 (ketone), C_{19} (hydroxy), and C_{26} (hydroxy). Some of these bryologs have binding affinity to PKC at the low nanomolar and even picomolar level and demonstrate greater potency than bryostatin 1 in in vitro cell line assays.[183−196]

Recently, the Wender group reported another very interesting activity of the bryologs. PKC has emerged as an interesting target for latent viral reactivation.[197,198] This reactivation is a particular problem in the treatment of HIV/AIDS with highly active antiretroviral therapy (HAART). Discontinuation of HAART results in viral rebound and disease progression. Prostratin, a plant-derived natural product, is a phorbol ester that is currently being advanced as a potential clinical candidate for latent viral reservoir clearance.[199−202] Bryostatin 1 and several synthetically accessible bryologs have been shown to be up to 1000-fold more potent in inducing latent HIV expression than prostratin.[203,204]

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Development of the bryologs is a compelling example of modern medicinal chemistry being used to optimize the bioactivity of a natural product lead. Thus, the bryologs represent exciting leads for the potential treatment of cancer, Alzheimer's disease, and HIV/AIDS.

Eribulin (2; Halaven, E7389). Due to its extraordinary antitumor activity, the antitubulin marine natural product halichondrin B (**60**) was chosen for preclinical development in 1992. Clinical development was severely impeded due to the limited amounts of compound available from natural sources.

Kishi's group reported the total synthesis for halichondrin B in 1992.[205] In collaboration with scientists at the Eisai Research Institute (ERI) in Woburn, MA, Kishi demonstrated that the right-hand macrolide half of the molecule (approximate molecular weight of 600) retained all or most of the potency of the much larger parent compound. Chemists at the ERI, working very closely with Kishi's group, synthesized over 200 analogues.[206,207] In conjunction with the Developmental Therapeutics Program (DTP) at NCI, they demonstrated that the modified truncated macrocyclic ketone eribulin (**2**, E7389), one of the last two compounds synthesized, had greater in vivo stability and possessed comparable bioactivity to and lower toxicity than the naturally occurring halichondrin B (obtained by DTP in conjunction with New Zealand scientists).

Subsequently, the Eisai group has demonstrated that relatively minor changes to the "tail" of the molecule resulted in much lower propensity for inducing P-glycoprotein susceptibility while retaining in vivo potency.[208] Incorporation of a morpholine in the "tail" demonstrated oral activity in a subcutaneous LOX melanoma model,[209] and modification by ring closure at the "tail" yielded a different morpholino derivative that demonstrated intravenous in vivo activity in an orthotopic murine model of a human glioblastoma.[210]

The development of eribulin (E7389), perhaps the most complex drug molecule yet produced by total synthesis, from a marine-derived antitumor agent, halichondrin B, is a compelling example of the power of the DTS approach.

Dysidiolide. A combinatorial library inspired by the marine natural product dysidiolide (**61**) demonstrates the power and potential of the BIOS approach. The Waldmann group postulated that the γ-hydroxy-butenolide group of dysidiolide was the major determinant of phosphatase activity. Testing of a 147-member library built around this molecule yielded a compound 10-fold more potent (IC_{50} = 350 nM) than the parent compound against the phosphatase Cdc25A.[211]

Their analysis of three-dimensional shape around the ligand-binding site, regardless of sequence similarity, classified Cdc25a within the same PSSC as the enzymes acetylcholinesterase and 11β-hydroxysteroid dehydrogenase type 1. Screening of the dysidiolide library against these two enzymes identified other library members having low micromolar activities against these additional targets,[212] thus demonstrating that simple changes in structure provide inhibitors of enzymes that would normally not be considered to be related in any way. Readers might also consult one of the latest publications from the Waldmann group, which demonstrates how simple tetrahydroisoquinolines using the BIOS approach demonstrate antitubulin activities.[213]

■ TARGETED THERAPIES

Introduction (Nominally Microbial, Marine, and Plant-Derived). A frequent liability of natural products, at least in the area of cancer chemotherapy, is that while many are potent cytotoxins, they have limited solubility in aqueous solvents and exhibit considerable toxicity, often resulting in a narrow therapeutic index. As a result, a number of pure natural products have failed as promising leads, including the plant-derived agents bruceantin and maytansine. An alternative approach to using such agents is the investigation of their potential as "warheads" attached to monoclonal antibodies specifically targeting epitopes on the tumor of interest. Such agents are called antibody drug conjugates (ADCs). The promise of this approach to cancer therapy has been the subject of several reviews[214−218] and a recent book chapter.[219]

Microbial. An early example of the use of the ADC methodology was the preparation of gemtuzumab ozogamicin (GO, Mylotarg) and inotuzumab ozogamicin consisting of a derivative of calicheamicin-γI_1 (**62**), a potent DNA-binding cytotoxic enediyne antibiotic,[220] linked to a humanized monoclonal IgG4 antibody directed against CD33 or CD22, specific markers of myeloid leukemias and B-cell malignancies, respectively.[221] Unfortunately, Mylotarg was withdrawn from market in the U.S. in June 2010 due to the observation of increased patient death with no added benefit over conventional cancer therapies. As of October 2013, inotuzumab ozogamicin remains in eight clinical trials, having completed six trials (http://www.cancer.gov/drugdictionary?CdrID=352004), and GO is still in use in Japan, having been approved in 2005.

Nominally Marine (Dolastatin 10 Derivatives. Brentuximab Vedotin). During the 1980s, over 20 dolastatins were isolated in minute quantities from the shell-less mollusk *Dolabella auricularia* collected in various locations, including off the coasts of Mauritius, Papua New Guinea, and Japan.[222,223] These novel linear and cyclic peptides exhibited potent cytotoxicity, acting through inhibition of tubulin polymerization, and dolastatin 10 was shown to be the most potent, with ED_{50} values in the subnanomolar range against a number of cancer cell lines. The development of efficient total syntheses afforded sufficient quantities for preclinical and clinical studies, but dolastatin 10 has not shown significant clinical activity as a single agent in 15 trials completed as of October 2013 (http://www.cancer.gov/drugdictionary?CdrID=42316). Structure−activity studies led to development of the synthetic derivative soblidotin (auristatin PE), which also advanced to two phase II clinical trials against soft tissue sarcoma and non-small-cell lung cancer, but no objective responses have been reported (http://www.cancer.gov/drugdictionary?CdrID=302644).[223]

Conjugation of a simple derivative, monomethyl auristatin E (**3**; MMAE, also known as vedotin), to the humanized anti-CD30 monoclonal antibody SGN-30 gives brentuximab vedotin (**63**, SGN-35; Adcetris), an ADC directed against the CD30 antigen expressed on Hodgkin lymphoma and anaplastic large-cell lymphoma.[224] Brentuximab vedotin has completed 10 clinical trials and is in 27 trials in hematological malignancies (http://www.cancer.gov/drugdictionary?CdrID=530758). In August 2011, it was granted accelerated approval by the FDA for treatment of relapsed Hodgkin lymphoma and relapsed systemic anaplastic large-cell lymphoma, with conditional marketing authorization being granted by the EMEA for the same indications in October 2012.

Nominally Plant (Maytansinoids). A promising candidate for the ADC targeting approach is maytansine (**64**), which was isolated in extremely low yield in the early 1960s from the Ethiopian plant *Maytenus serrata*.[225,226] Given its novel structure and very potent in vitro activity, further development was pursued, but despite the promising activity shown in preclinical animal testing, insignificant efficacy was observed in

human clinical trials, and studies were terminated in the early 1980s.

From the initial determination of its structure, natural product chemists wondered if the compound was microbial in origin due to its similarity to the "ansa" antibiotics, such as the rifamycins. In 1977, this speculation was strengthened by the isolation of the ansamitocins, which closely resembled the maytansinoids, from the bacterium *Actinosynnema pretiosum*.[225,227] Further highly circumstantial evidence for the bacterial source of the maytansinoids was given in a very recent paper by members of the Leistner group, who were able to identify a very closely related *Actinosynnema* sp. in the microbial root system of plants producing maytansine, coupled to the complete absence of a required AHBA synthase gene in plant cell cultures of the nominal host plant.[228]

The maytansinoid derivatives, DM1 (**65**) and DM4 (**66**), prepared from appropriate ansamitocins, can be conjugated through either thioether or disulfide linkages with various monoclonal antibodies targeting a variety of cancers.[225,226] T-DM1, or ado-trastuzumab emtansine, where DM1 is linked to the approved *Her2neu*-targeted antibody trastuzumab, is currently in 12 clinical trials (October 2013), either as a single agent or in combination other agents such as docetaxel or paclitaxel (http://www.cancer.gov/drugdictionary?CdrID=564399).

In February 2013, the FDA approved ado-trastuzumab emtansine (**67**, Kadcyla) as a new therapy for patients with *Her2*-positive, late-stage (metastatic) breast cancer, due to significant efficacy in the treatment of patients with advanced or metastatic *Her2*-positive breast cancer who had failed at least two treatments with the currently approved drugs, trastuzumab and the tyrosine kinase inhibitor lapatinib.[225,229−231]

SAR3419 (http://www.cancer.gov/drugdictionary?CdrID=574048), a novel anti-CD19 humanized monoclonal antibody conjugated to DM4, is in two clinical trials for the treatment of B-cell malignancies, having completed three trials.[232] A recent review by Teicher and Chari,[233] which should be read in conjunction with the article by Koehn,[219] gives the clinical status of these and several other ADCs. Thus, a bioactive natural product macrocycle that had failed clinical trials in the late 1970s has now become a potent and active treatment for specific breast cancers by using it as a warhead.

FUTURE PROSPECTS

The power of the ADC methodology in overcoming problems associated with potent cytotoxic natural products is clearly illustrated by the examples of the dolastatin and maytansine derivatives briefly discussed above. The development of similar strategies can be envisaged for other natural product leads. These include a range of antitumor agents in various stages of preclinical and clinical development, of which some have been dropped from clinical studies.[6] Other potential candidates include potent members of mechanistic classes, such as actin inhibitors (e.g., cytochalasins, jaspamide, and latruculin derivatives),[234] and tubulin inhibitors,[235] many of which are of marine origin and thus far have failed to advance to clinical studies.[236,237] In this respect, the success achieved by efficient total syntheses of complex natural products, such as marine-derived actin inhibitors[238] and spongistatin derivatives,[239] in overcoming serious supply problems associated with the low-yield isolations from natural sources can play a pivotal role.

In addition to the examples given above in ADCs based on warheads from marine sources, the number of potential plant-derived materials is also high, with materials that have been in preclinical and clinical trials for a variety of diseases over the last 50 plus years being potential candidates for this approach.

Another area that definitely needs new drugs and leads thereto is the antibiotic arena, including in particular new antifungal agents based on natural prroducts. What is of scientific interest is that there are no antimicrobial agents from plant sources that have been successful in reaching advanced clinical trials, even though major plant pathogens are microbial in origin. The reason(s) for this dearth of activity are not known, though it is interesting to point out that taxol is an antifungal agent as well. Thus a concerted effort to look at natural products from (nominally) plant and all other sources as leads to novel antimicrobials may well prove successful. It will probably be the case that such agents will have to be modified chemically in order to generate clinically relevant agents, but the base structure will almost certainly be from nature. An example of the major failure of combinatorial chemistry in this disease area is shown by the review paper from the GSK researchers published in 2007.[240] A further discussion of the problems by Livermore on behalf of the British Society for Antimicrobial Chemotherapy in 2011 is indicative of the methodologies that are now being investigated including modification of well-known classes of antibiotics and "persuasion" of established producing microbes to produce molecules that are products of currently unexpressed pathways. This latter technique could almost be considered as "repurposing of existing producers" rather than their current products and is now the focus of significant academic work.[241]

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Notes

The opinions expressed in this review are those of the authors and not necessarily those of the U.S. Government.

The authors declare no competing financial interest.

DEDICATION

Dedicated to Prof. Dr. Otto Sticher, of ETH-Zurich, Zurich, Switzerland, for his pioneering work in pharmacognosy and phytochemistry.

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